JP 49-048,663

Translated from Japanese by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

Code: 1505-70485

JAPANESE PATENT OFFICE
PATENT JOURNAL
KOKAI PATENT APPLICATION NO. SHO 49[1974]-48663

Japanese Cl.:	16 E362 30 B1 16 E431.1
Sequence Nos. for Office Use:	7242 44 6224 44 7169 44
Application No.:	Sho 47[1972]-91240
Application Date:	September 13, 1972
Publication Date:	May 11, 1974
	(Total of 7 pages)
Examination Request:	Not requested

PREPARATION METHOD OF 2-(SUBSTITUTED AMINO) IMIDAZOLES

Inventors:	Tamio Nishimura 23 Hikawa-cho, Itabashi-ku, Tokyo Hiroshige Toku 2-404 Seibu Mogusendanchi 898 Mogusa, Hino-shi, Tokyo
Applicant:	Tamio Nishimura 23 Hikawa-cho, Itabashi-ku, Tokyo
Agent:	Yoshio Fuwa, patent attorney

List of attached documents: (1) "Chemistry Letters 1972, No. 8 Contents"

(2) Paper published in the above journal, pp. 649-652

(3) Abridged translation of the paper in (2)

Mechanism of Voges-Proscawel Reaction

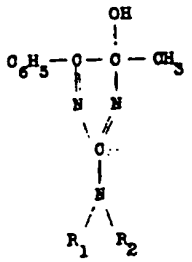
Tamio Nishimura, Hiroshige Toku, Tetsuro Ueno, Shinji Shibamoto, Toshio Imai

A hypothetical intermediate of pigments produced by the Voges-Proscawel reaction is synthesized from 1-methyl-1-benzyl guanidine and acetyl benzoyl and a coloration mechanism is proposed.

[Attached amendments have been incorporated into text of translation]

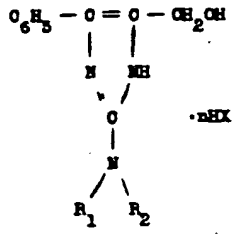
Claims

1. A preparation method for 2-(substituted amino) imidazoles, characterized by reacting acetyl benzoyl with substituted guanidine in the presence of solvents under inert gas to obtain 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazoles shown by



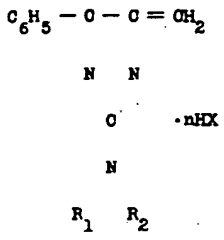
where R_1 and R_2 are independently hydrogen atoms, alkyls, alkylenes, or aralkyls.

2. A preparation method for 2-(substituted amino) imidazoles, characterized by dissolving 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazoles, which are obtained in Claim 1, in a dilute acid, refining, and concentrating on a steam bath in vacuo to obtain 2-(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazoles shown by



where R_1 and R_2 are independently hydrogen atoms, alkyls, alkylenes, or aralkyls; HX is an acid; n is an integer of 1 or 2.

3. A preparation method for 2-(substituted amino) imidazoles, characterized by dissolving 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazoles or 2-(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazoles, which are obtained in Claim 1 or 2, in a concentrated acid and allowing this to stand to obtain 2-(substituted amino)-4-methylene-5-phenyl-4H-imidazoles shown by



where R_1 and R_2 are independently hydrogen atoms, alkyls, alkylenes, or aralkyls; HX is an acid; n is an integer of 1 or 2.

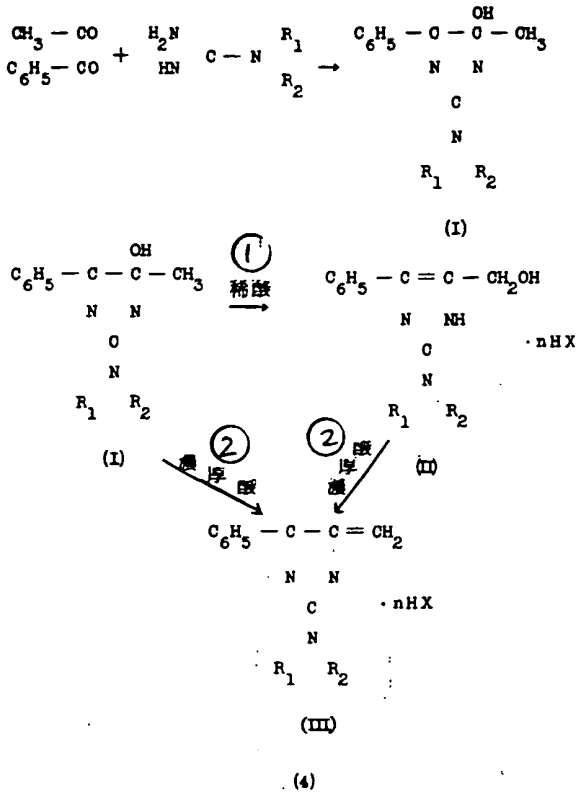
Detailed explanation of the invention

The present invention relates to a preparation method for 2-(substituted amino) imidazoles consisting of 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazoles, 2-

(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazoles, and 2-(substituted amino)-4-methylene-5-phenyl-4H-imidazoles.

The purpose of this invention is to prepare new compounds having medicinal effects and another purpose is to prepare intermediate compounds for manufacture of new bactericides, mildewcides, clinical test reagents, etc.

The reaction of this invention is carried out as follows.



Key: 1 Dilute acid
2 Concentrated acid

wherein R_1 and R_2 are independently hydrogen atoms, alkyls, alkylenes, or aralkyls; HX is an acid; n is an integer of 1 or 2. Namely, acetyl benzoyl is reacted with various substituted guanidines in a suitable solvent under inert gas to produce 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole (I). The addition molar ratio of acetyl benzoyl to substituted

guanidines is (1-5):1, and as the solvent water or alkanol, preferably water is used. Although this reaction is completed in 0.5-2 h, it is desired that the reaction be carried out under an inert gas such as nitrogen in order to avoid contact with oxygen during the reaction and separation of the product since the product (I) can be colored by oxygen. The product yield in this reaction varies with R_1 and R_2 in the substituted guanidines. When both R_1 and R_2 are hydrogens it is as low as about 5%, and when both R_1 and R_2 are alkyls, alkylenes or aralkyls, it is as high as about 70%. When one of R_1 and R_2 is hydrogen it is in between.

Next, if a dilute acid is added at room temperature after separating the 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole (I) from the reaction solution or without separating it, 2-(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazole acid salt (II) is produced. In this reaction, as the dilute acid, a mineral acid such as hydrochloric acid, sulfuric acid, nitric acid, etc., may be used, but hydrochloric acid is especially preferred. The addition amount of the acid is 2-15 moles per 1 mole of 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole (I), and it is preferred to adjust the acid concentration in the solution to less than or equal to about 10%. By this reaction, 2-(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazole in an amount of 30-60%, based on 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole (I), is obtained.

Furthermore, if 2-(substituted amino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole (I) or 2-(substituted amino)-4(5)-hydroxymethyl-5(4)-phenylimidazole (II), obtained by the aforementioned method, is dissolved in concentrated acid and allowed to stand at room temperature, 2-(substituted amino)-4-methylene-5-phenyl-4H-imidazole acid salt (III) will crystallize. In this reaction, a mineral acid such as hydrochloric acid, sulfuric acid, nitric acid, etc., is used as the acid, but 20-36%, preferably 36% hydrochloric acid is preferably used. The addition amount of the acid is about 3-50 mL per 1 g of raw material in the case of 36% hydrochloric acid. The standing time is 10-15 h at room temperature, and the product is obtained at almost quantitative yield.

All of 2-(substituted amino) imidazoles prepared by the present invention are new compounds and can be used as medicine. In addition, new bactericides, mildewcides, clinical test reagents, etc., can be manufactured from the compounds.

Application Example 1

Preparation of 2-(N-methyl-N-benzylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N-methyl-N-benzylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride

Acetyl benzoyl 1.48 g (0.01 mol) was dissolved in 500 mL water, mixed with a solution prepared by dissolving 1.63 g (0.01 mol) N-methyl-N-benzyl guanidine in 10 mL water, and reacted by stirring under nitrogen gas at room temperature. After reacting for 30 min, the product

was suction filtered without air contact, washed with cold water, and dried in a reduced pressure desiccator to obtain 1.20 g (yield 71%) 2-(N-methyl-N-benzylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole. This was a light green powder with a melting point of 147-8°C (decomposed). In addition, its IR_{KBr} cm^{-1} was 3070, 3040, 2960, 2840, 1630, 1590, 1580, 1450, 1360, 1150, 730, and 695.

Next, the product 293 mg (1 mmol) was suspended in 50 mL water, mixed with 5 mL of 10% hydrochloric acid, and concentrated and dried under a reduced pressure to a solid. Then, the solid was dissolved in ethanol by heating, refined by activated carbon, concentrated, and dried to obtain 200 mg of a yellow powder of 2-(N-methyl-N-benzylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride. It had a melting point of 161-2°C (foamed), and its IR_{KBr} cm^{-1} was 3040, 3020, 2980, 2920, 1665, 1620, 1580, 1545, 1455, 1365, 1035, 770, and 700.

Application Example 2

Preparation of 2-(N,N-pentamethyleneamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N,N-pentamethyleneamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride

Acetyl benzoyl 1.48 g (0.01 mol) was dissolved in 500 mL water, mixed with a solution prepared by dissolving 1.27 g (0.01 mol) N,N-pentamethylene guanidine in 10 mL water, and reacted by stirring under nitrogen gas at room temperature. After reacting for 30 min, the product was suction filtered without air contact, washed with cold water, and dried in a reduced pressure desiccator to obtain a light green powder of 2-(N,N-pentamethyleneamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole at a yield of 67%. It had a melting point of 136-8°C (decomposed), and its IR_{KBr} cm^{-1} was 3040, 2930, 2840, 1620, 1580, 1530, 1450, 1375, 1160, 755, and 705.

Next, the product 257 mg (1 mmol) was suspended in 50 mL water, mixed with 5 mL of 10% hydrochloric acid, and concentrated and dried under a reduced pressure to a solid. Then, the solid was dissolved in ethanol by heating, refined by activated carbon, concentrated, and dried to obtain 2-(N,N-pentamethyleneamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride at a yield of 40%. It had a melting point of 244-5°C (decomposed) (semifused at 160°C), and its IR_{KBr} cm^{-1} was 3040, 3020, 2930, 2850, 1665, 1645, 1610, 1600, 1550, 1455, 1065, 775, and 705.

Application Example 3

Preparation of 2-(N,N-dimethylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N,N-dimethylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride

Acetyl benzoyl 7.40 g (0.05 mol) was dissolved in 2000 mL water, mixed with a solution prepared by dissolving 0.87 g (0.01 mol) N,N-dimethyl guanidine in 10 mL water, and reacted

by stirring under nitrogen gas at room temperature. After reacting for 30 min, the product was suction filtered without air contact, washed with cold water, and dried in a reduced pressure desiccator to obtain a lemon yellow powder of 2-(N,N-dimethylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole at a yield of 70%. It had a melting point of 65-7°C, and its $IR_{KBr}cm^{-1}$ was 3040, 3020, 2970, 2920, 1620, 1600, 1580, 1450, 1360, 1175, and 740.

Next, the product 1 mmol was mixed with 5 mL of 10% hydrochloric acid, and concentrated and dried under a reduced pressure to a solid. Then, the solid was dissolved in ethanol by heating, refined by activated carbon, concentrated, and dried to obtain a white powder of 2-(N,N-dimethylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole at a yield of 50%. It had a melting point of 157-8°C, and its IR_{KBr} cm^{-1} was 3040, 3020, 2990, 2960, 1675, 1600, 1580, 1530, 1450, 1360, 1025, 770, and 700.

Application Example 4

Preparation of 2-(methylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole

Acetyl benzoyl 0.01 mol was dissolved in 770 mL water, mixed with a solution prepared by dissolving 0.01 mol dimethyl guanidine in 10 mL water, and reacted by stirring under nitrogen gas at room temperature. After reacting for 30 min, the product was suction filtered without air contact, washed with cold water, and dried in a reduced pressure desiccator to obtain a lemon yellow powder of 2-(methylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole at a yield of 29%. It had a melting point of 107-108°C (semi-fused at 98°C), and its IR_{KBr} cm^{-1} was 3040, 3020, 2970, 2920, 1640, 1590, 1575, 1445, 1355, 1155, 760 and 665.

Application Example 5

Preparation of 2-amino-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-amino-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride

Acetyl benzoyl 0.002 mol was dissolved in 75 mL water, mixed with a solution prepared by dissolving 0.002 mol guanidine in 10 mL water, and reacted by stirring under nitrogen gas at room temperature. After reacting for 30 min, the product was suction filtered without air contact, washed with cold water, and dried in a reduced pressure desiccator to obtain a white powder of 2-amino-4-hydroxy-4-methyl-5-phenyl-4H-imidazole at a yield of 5%. It had a melting point of 113-5°C (decomposed), and its IR_{KBr} cm^{-1} was 3040, 3020, 1645, 1590, 1540, 1445, 1355, 1160, 740, and 690.

Next, the product 1 mmol was mixed with 5 mL of 10% hydrochloric acid, concentrated, and dried under a reduced pressure to a solid. Then, the solid was dissolved in ethanol by heating, refined by activated carbon, concentrated, and dried to obtain a dark green powder of

2-amino-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride at a yield of 30%. It had a melting point of 166°C (decomposed), and its IR_{KBr} cm^{-1} was 3040, 3020, 1680, 1655, 1610, 1580, 1565, 1560, 1450, 1360, 1065, 765, and 700.

Application Example 6

Preparation of 2-(N-methyl-N-benzylamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride

2-(N-methyl-N-benzylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N-methyl-N-benzylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride, which were prepared in Application Example 1, 300 mg each were dissolved in 5 mL of 36% hydrochloric acid and kept overnight at room temperature to quantitatively obtain colorless plate-form crystals of 2-(N-methyl-N-benzylamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride, which had more gloss than either of the starting compounds. The melting point was 120°C, and the IR_{KBr} cm^{-1} was 2990, 2900, 2800, 2660, 1665, 1610, 1590, 1455, 1430, 1370, 930, 770, and 700.

Application Example 7

Preparation of 2-(N,N-pentamethyleneamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride

2-(N,N-pentamethyleneamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N,N-pentamethyleneamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride, which were prepared in Application Example 2, 200 mg each were dissolved in 5 mL of 36% hydrochloric acid and kept overnight at room temperature to quantitatively obtain colorless plate-form crystals of 2-(N,N-pentamethyleneamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride. The melting point was 266°C (decomposed), and the IR_{KBr} cm^{-1} was 2930, 2840, 1610, 1600, 1580, 1465, 1455, 1422, 905, 775, and 700.

Application Example 8

Preparation of 2-(N,N-dimethylamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride

2-(N,N-dimethylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-(N,N-dimethylamino)-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride, which were prepared in Application Example 3, 300 mg each were dissolved in 5 mL of 36% hydrochloric acid and kept overnight at room temperature to quantitatively obtain a white powder of 2-(N,N-pentamethyleneamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride, which was whiter than either starting material. The melting point was 94-6°C (semifused at 86°C), and the IR_{KBr} cm^{-1} was 2990, 2930, 1685, 1610, 1600, 1450, 1390, 1360, 930, 770, and 700.

Application Example 9

Preparation of 2-(N-methylamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride

2-(Methylamino)-4-hydroxy-4-methyl-5-phenyl-4H-imidazole, which was prepared in Application Example 4, 300 mg was dissolved in 5 mL of 36% hydrochloric acid and kept overnight at room temperature to quantitatively obtain a light green powder of 2-(N-ethylamino)-4-methylene-5-phenyl-4H-imidazole dihydrochloride. The melting point was 113-4°C (semifused at 89°C), and the IR_{KBr} cm^{-1} was 3000, 2940, 1680, 1620, 1600, 1450, 1410, 1360, 920, 765, and 700.

Application Example 10

Preparation of 2-amino-4-methylene-5-phenyl-4H-imidazole dihydrochloride

2-Amino-4-hydroxy-4-methyl-5-phenyl-4H-imidazole and 2-amino-4(5)-hydroxymethyl-5(4)-phenylimidazole dihydrochloride, which were prepared in Application Example 5, 300 mg each were dissolved in 5 mL of 36% hydrochloric acid and kept overnight at room temperature to quantitatively obtain a light green powder of 2-amino-4-methylene-5-phenyl-4H-imidazole dihydrochloride. The melting point was 175-176°C (foamed), and the IR_{KBr} cm^{-1} was 3090, 1685, 1565, 1550, 1375, 1340, 770, and 710.